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E11-04 Controversy in Small Cell Lung Cancer, Tue, Sept 4, 16:00 – 17:30

The role of irinotecan in the treatment of small cell lung cancer

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Since the 1960's, small cell lung cancer (SCLC) has been recognized as a distinct subtype of lung cancer with a unique sensitivity to chemotherapy (1). Multiple therapeutic agents and strategies tested over the last 3 decades result in a 1 year survival rate of 30-40% for patients with extensive stage disease (ED). Unfortunately, unlike other chemotherapy-sensitive cancers such as lymphoma and germ cell tumors, significant advances in the treatment of ED SCLC have stalled. Testing of "newer" chemotherapy agents such as epirubicin, ifosfamide, vinorelbine, the taxanes, and gemcitabine, have failed to improve survival compared with the older chemotherapy agents, cisplatin and etoposide (PE). In the U.S. PE for 4 cycles has been standard first line therapy based upon the results of randomized trials which indicated that other regimens were not superior, but rather resulted in more inconvenience and toxicity (2).

Camptothecin is a plant alkaloid present in the Asian tree Camptotheca acuminata. Camptothecin was recognized as a potential anti-cancer drug based upon a screening program conducted by the U.S. National Cancer Institute in the 1960's (3). During replication, DNA unwinds so that single strands serve as a template for synthesis of new DNA strands. Topoisomerase 1 plays a critical role in the cleavage of single DNA strands, necessary to allow the broken strand of DNA to rotate around the intact strand during DNA replication. Camptothecins target topoisomerase 1 by stabilizing the cleavable complex between topoisomerase 1 and DNA (4). Irinotecan, a water-soluble semi synthetic derivative of camptothecin, entered clinical trials in the 1980's. Irinotecan is a prodrug of the metabolite, SN38, which has 2-3 logs greater activity than irinotecan. Importantly, SN-38 is cleared by uridine diphosphate glycosyltransferase 1 family polypeptide A1 (UGT1A1), an enzyme important for biliary glucuronidation. Patients with certain polymorphisms in the promoter region of UGT1A1 are at higher risk for diarrhea and neutropenia (5).

In 2002, Noda et al reported the results of a phase III trial from the Japanese Cooperative Oncology Group (JCOG) that compared treatment with cisplatin plus either irinotecan or etoposide in 154 patients with ED SCLC (6). Median and 1 year survival was significant improved in the patients receiving the irinotecan-based regimen compared with PE (12.8 months vs. 9.4 months, 58.4% vs. 37.7%, respectively). Patients on the PE arm experienced more neutropenia and thrombocytopenia, while patients on the IP arm experienced more diarrhea. The study was discontinued early based upon the recommendation of a data monitoring committee. A phase III trial conducted in the U.S., Canada, and Australia, utilizing a different dose and schedule of irinotecan and cisplatin failed to confirm a survival advantage for the IP arm over the EP arm (7). Despite a change in the dose and schedule of IP, rates of gastrointestinal toxicity, namely vomiting and diarrhea were not substantially reduced, although dose intensity was improved compared with the IP regimen utilized in the JCOG trial. While there are several plausible reasons to explain the disparate results from the two trials, known pharmacogenomic differences between North American and Japanese populations likely played a role in determining both toxicity and efficacy profiles of IP. Specifically, polymorphisms in UGT1A1 are observed between patient populations. Low rates of Gilbert's syndrome (decreased level of gene transcription of UGT1A1) are recognized in Asian populations (8). In one study in non-small cell lung cancer, patients with Gilbert's syndrome experienced more toxicity and worse survival with IP (9). Differences in toxicity and efficacy profiles amongst North American and Japanese patients utilizing the same drugs have been reported (10). Similarly, UGT1A1*6 and UGT1A9*22 genotypes have recently been reported to be associated with irnotecan-related toxicity, response, and survival in Korean patients (11).

While PE remains standard in the U.S. for now, IP is an equally effective alternative regimen against ED SCLC. The substitution of carboplatin for cisplatin in the IP regimen has been explored in phase II and randomized phase II studies. Progression free survival favored

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carboplatin plus irinotecan over carboplatin plus etoposide in one study (12). Other randomized trials comparing these carboplatin-based regimens are being conducted. Furthermore, a phase I trial combining cisplatin plus etoposide plus irinotecan resulted in a 77% response rate and median survival time of 12 months in 31 evaluable patients from Greece (13). Further phase II/III evaluation of this three drug regimen are underway. Finally, irinotecan-based therapy is undergoing evaluation in limited stage patients as induction therapy (IP followed by concurrent EP and radiation) as well as consolidation therapy (EP and concurrent radiation followed by IP) (14,15). Each of these strategies resulted in a median survival time of about 2 years in phase II studies.

In conclusion, irinotecan is an active drug against SCLC. The IP regimen appears more effective than EP in Asian patient populations, although these results have not been confirmed in North American populations. A completed phase III study from the Southwest Oncology Group in the U.S. comparing IP versus EP, given in the identical dose and schedules as the Noda trial, will definitively address this issue. Studies evaluating the role of irinotecan in limited stage disease are underway.

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Session E12: Recent Advances and Future Prospective in Lung Cancer Pathology

E12-01 Recent Adv and Future Prospective in LC Pathology, Tue, Sept 4, 16:00 – 17:30

NCI Director's challenge gene profiling of lung adenocarcinomas: impact on histologic classification

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Despite the remarkable advances in the molecular biology of lung adenocarcinoma, surprisingly few studies are supported by carefully detailed pathologic data. Lung adenocarcinoma histologic subtyping continues to evolve following the 2004 WHO classification. [1] The search for a clinically and biologically meaningful way to further characterize the mixed subtype adenocarcinomas needs to be based on careful attention to the histologic criteria being applied so the data can be compared to other studies. There are widely varying published results regarding the correlation of histologic subtypes with different molecular features including EGFR, k-RAS and gene expression profiling. The methods of some of these papers indicate varied pathologic definitions, suggesting that some of these differences may be attributed to interpretation of the histologic subtyping. Most articles also focus on a single subtype of lung adenocarcinoma, mostly bronchioloalveolar carcinoma (BAC), comparing this with all other adenocarcinomas. Future molecular studies of lung adenocarcinoma should be accompanied by careful histologic subtyping of the tumors with attention not only to a single component such as BAC, but all histologic subtypes, noting the predominant pattern in mixed subtype tumors.

Correlations between histology and molecular findings also vary depending whether the study involves non-small cell carcinoma or purely adenocarcinoma. For example associations between EGFR mutations and non-smokers, female gender, Asian descent, and adenocarcinoma, particularly with BAC, are generally much stronger if all non-small cell carcinomas are studied. These correlations are often not as strong in studies of pure adenocarcinoma.

While there is much emphasis in the literature about BAC and EGFR mutations, [2; 3] Tsao AS, Shigematsu H, Yoshida Y and Yatabe Y showed a lack of association of EGFR mutation with BAC subtype suggesting an association with invasive adenocarcinoma rather than BAC. [4-7] Kim, YH et al found that a dominant papillary subtype is a significant predictor of response to gefitinib in adenocarcinoma of the lung. [8] K-ras mutations are associated with 73-100% of the mucinous type of BAC. [9]

Gene profiling studies using cDNA arrays have consistently identified 3-4 clusters among of lung adenocarcinomas. [10-12] This is a powerful tool that can measure the expression of thousands of genes in a single tumor sample, allowing for identification of clinically and biologically subsets of tumors that are not apparent by usual clinical or pathologic methods. [13] Numerous studies have examined gene expression in a variety of subsets of lung cancer patients including non-small cell carcinoma, [14-20] adenocarcinoma, [10-12; 21-31] squamous cell carcinoma, [23; 26; 32; 33] and small cell carcinoma. [34] Gene expression profiling of lung cancers has been used to identify sets of genes that predict prognosis, [10; 17; 21; 25; 31; 32; 35-37] smoking status, [38] likelihood of metastases to lymph node[15; 18; 29] or brain[39], effectiveness of chemotherapy, [15; 40-42] tumor-stromal interactions, [43; 44] and differential diagnosis with other tumors such as malignant mesothelioma. [45] In addition to cDNA microarrays, other

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